

USSN 09/050,359

fixed position, said less variable codon encoding the second position of each peptide

each library being a separate and physically distinct entity from the other libraries of the panel.

REMARKS

1. Request to Vacate and/or Withdraw Finality

The office action mailed September 21, 2001 states that claims 22, 25, 28 and 29 are anticipated by or obvious over Pinilla et al., "for the reasons set forth in the previous actions".

However, all of these claims are directly or indirectly dependent on claim 31, which was not so rejected. There is thus an inconsistency.

The office action should be vacated and a new action mailed which either

- (1) withdraws the aforesaid rejections of claims 22, 25, 28 and 29 (OA §§17, 18) or
- (2) specifically applies the rejection to claim 31.

In this regard, we note that the previous action had also rejected claim 31.

2. Utility (OA §§11-12)

Claims 22, 25-30, 32-38 have been rejected under 35 USC §101 and 112 ¶1 for alleged lack of patentable utility.

Applicants have asserted that their structured panel of combinatorial peptides is useful both directly in the identification of peptides which bind targets, and, indirectly, in the identification of small organic compounds which bind the same targets.

The Examiner has questioned whether either of these is a "substantial" utility, this is, a utility that has a "real world" use.

Here, the Examiner fails to distinguish between the utility of the panel as a whole, and the utility of an individual peptide included in that library. A claim to an individual peptide would not meet the utility requirement until a use for that specific peptide was known, e.g., that it bound a target of known biological activity. But we are claiming a structured panel of peptides that has been carefully designed so as to facilitate the identification of target-binding peptides and other target-binding molecules. The structured panel of libraries is a research tool.

The Examiner suggested that research tools are only those which are usable "to evaluate materials other than themselves".

However, we must be careful in interpreting what is meant by "other than themselves". An individual peptide is something other than a peptide library, especially if the peptide library is displayed on phage and the individual peptide is in free form. Thus, we would say that the claimed libraries are useful as "research tools" in evaluating the ability of individual peptides to bind to a particular target.

This is different from saying that the utility of a compound is in determining the properties of that very compound.

Moreover, the specification plainly discloses that the panels of peptides may be used to identify non-peptide compounds which bind a target. The basic procedure is set forth at page 17, line 33 to page 18, line 11. The ultimately useful compound is the one from the "complementary library", not the original library. Thus, one could screen a peptide library to find peptides that bind the target, and then screen a benzodiazepine library (see page 39, line 11 to page 40, line 29) for benzodiazepines that inhibit the binding of the peptide (in labeled form) to the target. Plainly, a benzodiazepine is not a peptide. Thus, the peptide libraries are useful as research tools, in determining which benzodiazepines, carbamates,

pyrrolidines, piperazines, etc. (see page 40, line 30 to page 44, line 11) might mediate the biological activity of the target.

As evidence that peptide libraries have a "real world" utility, we submitted evidence of the commercial availability of peptide libraries from New England Biolabs, Invitrogen, Novagen, Display System Biotech, and Stratagene.

In response, the Examiner said, in the paragraph bridging pp. 3-4 of the June 19 action,

Applicants' arguments as to the pragmatic proof of the practical utility of combinatorial libraries is that such libraries are commercially bought and sold. Applicants rely upon the England Biolabs catalogue to show the commercial availability of a library kit. Applicants are not claiming a kit. Furthermore, all of these kits relate to a particular type of library unlike the instantly claimed undefined, unstructured etc. library. There is nothing of record that the alleged commerciality was not due to business events extraneous to the merits of the claimed invention. [See further Lebl et al (Biopolymers (at e.g., page 177, Library techniques to page 178, col. 1.)

We would be happy to rephrase these "panel" claims as "kit" claims. As previously explained, a "panel" is really a kind of kit. The Examiner says that this is not persuasive, but does not explain why. A "kit" is a plurality of components sold together which are intended to be used cooperatively. In our panel, each library is a component of a kit. The screening of the libraries provides information as to the peptide binding characteristics of a target substance; all must be screened for the sequence space to be fully explored.

The NEB kit consists of a X_7 , X_{10} or C- X_7 -C library (displayed on phage), gIII sequencing primer, a host E. coli strain, control target and eluant, and detailed protocols. It is quite clear from the sales literature that the single most

commercially important component of the kit is the library per se.

Moreover, there are libraries which have been sold by themselves, rather than as part of a kit, see, for example, Novagen's Pre-Made T7 SelectTM Libraries (Exhibit A).

The Examiner asserts that the libraries which were sold were of a "particular type". If by this he means that they were "purpose-built", that is certainly not true. The Ph.D.-7 library is (Xaa)7, and the Ph.D.-12 library is (Xaa)12. Thus, unbiased libraries have been sold. It is true that the variable residues are fused to a carrier phase protein moiety, but the use of a different carrier moiety (which our claims do not require) would not alter the utility, as long as display was still achieved. Our structured panel, like the unbiased libraries that were sold, allows a full exploration of diversity for genetically encoded peptides of a given length.

We are perplexed by the Examiner's reference to "business events extraneous to the merits of the claimed invention". If we were touting the commercial success of the claimed invention as objective evidence of nonobviousness, it would be relevant to ask whether that success was attributable to the superiority of the invention, or to favorable pricing or unusual marketing efforts. Here, we are simply trying to show that peptide libraries as a class have real world utility. Whether they are priced high or low, one assumes that they would not be bought if they lacked real world utility.

The Brenner-Kirk-Joly trilogy held that if a chemical was not patentably "useful", then a process for making only that chemical, or starting materials and intermediates useable only in such a process, likewise are not patentable. Moreover, if a chemical lacks a §101 utility, then a claim to a method of using that chemical would necessarily be unenabled under §112.

Nonetheless, the PTO has issued numerous patents to

libraries per se, as well as to methods of making or using libraries¹ and this, too, is evidence that there is a consensus that libraries are patentably useful.

The following cases illustrate the relevance of prior patents:

Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);

In re Chakrabarty, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);

Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);

In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply

¹ As of February 5, 2001, there are 907 U.S. and foreign "molecular diversity" patents listed at <http://www.5z.com/divinfo/patents.html>, most being U.S. Patents. Counsel's non-exhaustive search on the USPTO database (as of February 20, 2001) revealed 677 patents with specified combinations of particular keywords in the claims (Ex. B).

Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

We have successfully screened our peptide libraries, and identified peptides which bind several targets. These include targets for which there is a commercial market for binding molecules:

| | |
|---|---|
| Protein Kinase CβII - | Panvera sells isoform-specific polyclonal antibodies for cell biology research, www.panvera.com . |
| human MDM2 - | Santa Cruz Biotechnology sells polyclonal antibodies for research purposes, www.scbt.com (Ex. D); recent publication of a fungal metabolite, chlorofusin, that antagonizes binding of p53 to MDM2, Duncan et al., (2001) J. Am. Chem. Soc. 123:554-560. (enclosed Ex. C). |
| E coli ProRS - | reagents available under the generic class of aminoacyl-tRNA synthetase enzymatic assay: tRNA, amino acids sold by Sigma, www.sigma-aldrich.com (enclosed Ex. E). |
| H influenzae TyrRS - | See above for aminoacyl-tRNA synthetase |
| beta-glucosidase - | Sigma sells a variety of substrates and inhibitors (see enclosed Ex. F) |
| carboxypeptidase (B) - | Sigma sells substrate, hippuryl-Lys, and inhibitor protein (enclosed Ex. G) |
| alcohol dehydrogenase - | Sigma sells substrates β -NAD(H) and chemical inhibitors 4-Methylpyrazole |

Hydrochloride and Tetraethylthiuram disulfide (enclosed Ex. H).

biotinylated ProRS - see above for aminoacyl-tRNA synthetase

Estrogen Receptor - Panvera sells Fluormone™ ES2, a fluorescein-labeled estrogen ligand, and polyclonal antibodies to α & β isoforms; see enclosed for multiple applications (e.g., HTS, research) and details (Ex. I).

With regard to our showing of the commercial sale of libraries, the examiner now says at page 5, lines 3-9:

Applicants arguments regarding the 'real world' utility has been considered but is not persuasive. Applicants argue that peptide libraries from New England Biolabs, Invitrogen, Novagen, Display System Biotech and Stratgene are commercially available. This is not persuasive because the libraries sold are used in further research to identify specific proteins, and these libraries have defined libraries, which are different from the unstructured libraries of the instant claims. Applicants arguments that the panels are a kind of kit is not persuasive. The rejections of record have been maintained.

We find several of the examiner's comments to be puzzling. The Examiner says that the quoted libraries are "used in further research to identify specific proteins". Actually, they are screened to identify peptide members of the library which bind a target protein of interest. That is one of the disclosed uses of our library.

It is true that in a peptide phage library, the random peptide is linked to a coat protein to form a fusion protein. However, the linkage is made in such a manner that the coat

protein is unlikely to affect the binding of the "business end", the peptide insert. If a phage binds, it is the sequence of the peptide insert which is determined, and it is the peptide which is the subject of further research. So the identification of the binding fusion protein is ancillary to the identification of the peptide per se.

The Examiner also says that the libraries are "defined" libraries. The usual meaning of this term is a library in which some residues are constant and others are variable, such as the biased combinatorial peptide libraries disclosed herein. Those skilled in the art would characterize the New England Biolabs Ph.D.-7 (Xaa₇) and Ph.D.-12 (Xaa₁₂) libraries as undefined libraries, even though the linkers (GGGS) and the coat protein sequences are "defined".

We are surprised by the characterization of our libraries as "unstructured". First of all, our claims 26 and 27 recite displaying our peptides on viruses, which would imply that the peptides are fused to a viral coat protein. Hence, some of our libraries are defined in that sense (which is the only sense in which the Ph.D-7 and Ph.D-12 libraries are "defined").

However, we think it more important that our libraries are "defined" in the sense that, in each library, there is one constant position (claims 27 and 30) or two constant positions (claims 32-38). These make each library a "defined" library.

We are not persuaded, by the way, of the relevance of the "defined"/"undefined" distinction to utility. Traditionally, undefined (wholly random) libraries were screened when one had no idea of what peptides might bind the target of interest. Defined (partially random) libraries were screened when the target had a known binding motif. For example, HPQ occurs in most streptavidin binding peptides (P26, L34-37), so to identify additional peptides which bind streptavidin, one might screen a library like X₅-HPQ-X₅.

When peptide libraries are sold commercially, they are intended to appeal to the broadest possible range of customers, and hence usually are not biased toward binding a particular target. However, that does not mean that a biased library lacks utility. Rather it is more useful than an unbiased library, but to a more limited range of customers. A structured panel of biased library has the same broad utility as an unbiased library, but its screening provides more information.

Our libraries would be used the same way that the commercial libraries are used: to screen those libraries for members which bind a target of interest.

Another commercially available random peptide library is Clonetech's MATCHMAKER. "Each clone in the library expresses a different 16-residue random peptide fused to the activation domain (AD) of the yeast GAL4 transcriptional activator", see attached Exhibit. This plainly is a less defined library than the claimed ones, yet its utility is evidenced by its commercialization.

The peptide libraries which are available for sale are not limited to phage display libraries. For example, the DIVERSE-QUEST hexapeptide libraries are mixtures of random hexapeptides in solution. At each position, the peptide may have any of 19 different amino acids (cysteine is excluded). Thus, there are 19^6 , or 49,521,980 different sequences. Two libraries are offered; one synthesized with natural L-amino acids and the other with their D-stereoisomers.

There are two other DIVERSE-QUEST libraries of note. One is of 16 a.a. peptides with four random positions, the 12 nonrandom positions constraining the peptides into a beta-hairpin conformation. The other is of 17 a.a. peptides with four random positions, the nonrandom positions constraining the peptides into an alpha-helix conformation.

If, as asserted by the Examiner, a library of peptides is

not a "research tool", but merely a "subject of basic research", then the USPTO should not issue any patents on such libraries. Nor should it issue any patents on methods of making such libraries (the method would be useful only if the product is useful) or on methods of using such libraries.

However, the USPTO has issued hundreds of patents relating to combinatorial libraries.² Each of the applicants thought that their technologies had sufficient commercial utility to warrant the expense of drafting, filing and prosecuting a patent application. Each of the examiners thought that the application disclosed and claimed a patentably useful invention, or the patent would not have been issued.

A search on the PTO database for "peptide and (library or libraries)" generated 14,594 hits. Adding the limitation "phage" brought the number down to 8,834 hits. Adding instead "(random or stochastic or combinatorial)" still resulted in 8,586 hits. And there are patents which relate to libraries which do not use that term.

"Xaa" would be used in a sequence listing for an undefined amino acid. There are 3,700 U.S. patents with at least one "Xaa"; 1,245 with "Xaa Xaa" (this would not catch the use of two non-consecutive Xaa's); 710 with "Xaa Xaa Xaa"; 503 with "Xaa Xaa Xaa Xaa"; 402 with five consecutive Xaa's; 321 with six; 267 with seven; 228 with eight; 178 with nine; and 162 with ten consecutive Xaa's. No doubt there are longer undefined sequences, too.

Clearly, there is a consensus in the art that random peptide libraries are useful.

We also teach that the binding peptides identified by

² For a helpful compilation, see "Patents in Molecular Diversity", at <http://www.5z.com/divinfo/patents.html>. As of October 9, 2001, 847 U.S. and foreign patents and published applications were listed.

screening our peptide libraries can subsequently be used as surrogate ligands in screening non-peptide libraries for substances which inhibit peptide target receptor binding and hence are likely to act as antagonists of the natural agonists of the target receptor. The Examiner argues that further research would be needed to identify the utility of the non-peptide compounds. The Examiner misses the point. We are not claiming the nonpeptide compounds; rather, we claim the peptide library. If the peptide library is useful in evaluating a material other than itself, then it is a "research tool" and useful as such. Plainly, a nonpeptide compound is a material other than a peptide library. The definition of a "research tool" does not require that the evaluated material be shown to have utility. (And the ability to bind a target is itself useful as the ligand can then be immobilized and used in purifying the target. The disclosed target receptors are certainly useful.)

Moreover, we would point out that the preferred nonpeptide libraries are of chemical classes (e.g., benzodiazepines) known to have pharmacological effects,³ and may well include known antagonists of the target receptor.

In conclusion, the Examiner says that "research tools" are entities which are useful "to evaluate materials other than themselves", and that our libraries do not qualify. However, we argued that a library of 10^6 peptides is not the same material as a single purified peptide and hence can be considered a "research tool". Moreover, we use the peptides as surrogates (research tools) in screening a non-peptide library. Traditionally, the courts have taken a permissive view of §101 utility. Brenner was one of the few cases to find a lack of §101 utility, but it addressed the utility of a single compound, not of a library of

³ For benzodiazepines, see page 39, lines 11-20. Other examples would be hydantoins, see P40, L37-P41, L11 and P46, L20, and iperazines, see P43, L6-9 and P48, L21.

thousands or millions of compounds. We believe that in view of the extensive patent activity in this area, and the commercial availability of combinatorial libraries of various sorts, it is plain that the claimed libraries and panels of libraries have practical, "real world" utilities that satisfy 35 USC §101.

3. Description (OA §13-14)

In general, please see page 12-13 of our March 28, 2001 amendment.

The Examiner says "the sequence in page 25, line 25 does not specifically teach that the AA (same amino acid for all peptides in the library) is in the middle 50% of the sequence". The sequence refers to an "AA₁" as the constant AA, see line 31. At page 25, lines 35-38, the specification explains

Preferably, AA₁ is located at or near the center of the peptide. More preferably, AA₁ is either (a) at least five residues from both ends of the peptide, or (b) is in the middle 50% of the peptide. [emphasis added]

The Examiner is plainly mistaken.

4. Definiteness (OA §15-16)

See pp. 9-12 of our last amendment. Rejections C, D and F were withdrawn (OA §9) so only A, B and E remain. See OA §9.

4A. The Examiner has not responded to our explanation of why claims 32 and 33 are not omnibus claims. We further wish to point out that the USPTO has granted generic claims to peptide libraries.

In the Holmes patent (US 5,770,456), claim 1 reads:

An array of cyclic nucleic acids on a substrate, said nucleic acids having N nucleotide positions, said substrate comprising N different sites, said substrate sites comprising said cyclic nucleic acids coupled thereto, said cyclic nucleic acids comprising common nucleotide sequences but

coupled to said substrate at a different one of said nucleotide positions via a tether molecule in each of said different substrate sites.

4B. The Examiner questioned the meaning of "fixed", "screenable" and "structured panel".

"Fixed". The Examiner asserts that the term "fixed" is unclear in the absence of any peptide sequence. We do not understand why this would be the case. Claim 31 recites "each library having one and only one constant residue at a position fixed for all peptides in all libraries of said panel".

Consider a panel of the following libraries:

- (1) Xaa Xaa Trp Xaa Xaa
- (2) Xaa Xaa Pro Xaa Xaa
- (3) Xaa Xaa Tyr Xaa Xaa.

Position 3 would be a fixed position satisfying the criterion of claim 31, as quoted above. That is, it is the position of the constant residue in each of libraries 1-3.

That is not the case if the panel were of these libraries:

- (1') Xaa Trp Xaa Xaa Xaa
- (2') Xaa Xaa Pro Xaa Xaa
- (3') Xaa Xaa Xaa Tyr Xaa.

The aforementioned fixed position limitation would not be satisfied, as position 2 would be the constant residue position in library 1', position 3, in library 2', and position 4, in library 3'.

If one knows the amino acid reactants used at each step in the synthesis of a library, one may readily ascertain which steps added constant residues (by reaction with a pure AA) and which, variable ones (by reaction with an AA mixture). Moreover, even without such knowledge, one may surmise the identity of the constant and variable positions by sequencing a sampling of the peptides in the library. As few as 20 peptide sequences would

provide a reasonably reliable identification assuming that only 20 amino acids were used at each position and that equal proportions were strived for.

If this analysis were repeated for each library in the panel of libraries, one could readily ascertain whether there is a particular residue position which (1) is constant within a given library and (2) variable from library to library.

The term "fixed" position or residue is used in several U.S. Patents, evidencing that it is not inherently confusing.

In Olivera, USP 5,885,780, with claims to a method of constructing a conotoxin-like peptide library, the main claim does not recite the length of the peptides, or define any positions. It merely requires that the peptides be "small, rigid, conotoxin-like peptides having Cys residues arranged to allow formation of multiple disulfide bonds characteristic of naturally occurring conotoxins but with remaining amino acids being variable in sequence. Claim 7 requires that "the specified codons for Cys are in fixed positions characteristic of a natural conotoxin peptide sequence having disulfide bonds defining a 2-loop structure framework" (emphasis added). Claim 10 similarly refers to a 4-loop structure framework, and claim 13 to a 3-loop framework.

In Spatola, US 6,008,058, with claims to a method of synthesizing and screening a cyclic peptide library, the length is specified as 4-12 a.a. The peptides must comprise a trifunctional AA as its side chain is used to couple the cyclic peptide to a support. Otherwise, the sequences are undefined. Step (i) of claims 11 and 18 require a fixed AA at a single position.

Cook, USP 5,587,471 relates to a method of preparing a "random phosphate linked oligomer library" which is of an unspecified "desired length" and where the randomization is by reaction with a mixture of monomers unspecified save that they

be "chemically suitable" with respect to a "predetermined parameter". Claims 7 and 16 require "incorporating at least one fixed position in said growing oligomer".

In the Cantley patent (US 5,532,167), claim 4 recites a degenerate peptide library which "comprises peptides comprising a formula: $(Xaa)_n-Zaa-(Xaa)_m$ ". Claim 1 refers to "a phosphorylatable amino acid residue at a fixed non-degenerate position" (emphasis added).

While the Examiner cites a Pinilla article, there is also a Pinilla patent (5,556,762) on scanning libraries. Since this patent relates to a "scanning library", it is interesting to see how Pinilla set forth the concept of a panel of libraries which differ as a result of the "scanning" (shifting) of the position of a constant residue from library to library. Pinilla's "scanning" position is equivalent to our "second position" (claim 32). Pinilla claim 13 reads⁴:

13. A process for providing a six amino acid residue sequence of an oligopeptide ligand that specifically binds to an acceptor that comprises the steps of:
(a) providing six separate pluralities of sets of self-solubilizing, unsupported mixed oligopeptides, each of said pluralities having sets that consist essentially of a mixture of equimolar amounts of linear oligopeptide chains containing six amino acid residues in each chain, the members of each set having one of at least ten predetermined amino acid residues at a single, predetermined position of the oligopeptide chain, and having the same at least ten different amino acid residues at the same other positions of the oligopeptide chain, each set of a plurality of sets having equimolar amounts of at least ten different amino acid residues at said other positions in the oligopeptide chain but

⁴ Pinilla claim 1 is broader but more difficult to understand.

differing in that the one of the at least ten predetermined amino acid residues present at the predetermined chain position within each set is different between the sets, and each of the plurality of sets differing from the other pluralities of sets by the position of the one of at least ten predetermined amino acid residues present at the predetermined chain position within each set is different between the sets, and each of the plurality of sets differing from the other pluralities of sets by the position of the one of at least ten predetermined amino acid residues in the oligopeptide chain

(b) separately admixing each set from a first plurality of sets with said acceptor in an aqueous medium at a concentration of about 1 milligram per liter to about 100 grams per liter, separately assaying the binding of each set to said acceptor and determining the one or more sets that provided specific binding that plurality of sets; and

(c) repeating step (b) using each of the remaining pluralities of sets in place of said first plurality of sets;

wherein the identity and position of the amino acid residue of said each one or more sets that provided specific binding for each plurality of sets provides the six amino acid residue sequence for said ligand that specifically binds to said receptor.

Thus, what he calls a "set", we call a "library". What he calls "separate pluralities", we call "subpanels". What he calls a "predetermined position", we call our "second position", although his claim literally allows this to be a variable AA even within one set.

The analogy of Pinilla claim 13 to our claim is not perfect, but certainly it shows that one can define a combination of libraries on the basis of the library-to-library variation in the identity and position of a residue constant within a given library.

"Screenable". We agree with the examiner that "screenable" means "capable of being screened", and not that "the library is screened". Since the meaning is clear, the term is not indefinite.

The word "screenable" appears as part of the phrase "each library being a separately screenable and distinct physical entity from the other libraries of the panel". If our libraries were mixed together, then they would lose that distinctness⁵ and one would have a single library, rather than a structured panel of libraries.

It occurs to us that if each library is a separate and distinct physical entity from the other libraries of the panel, it is inherently "separately screenable", and the term "screenable" is then superfluous. Hence, we have deleted it for this reason rather than for the reason set forth by the examiner.

"Structured panel". We agree that "structured panel" is not an art-recognized term, but an inventor may serve as his own lexicographer. The term is formally defined at page 10, lines 1-8:

A "structural panel" is a panel as defined above where there is some structural relationship between the member libraries. For example, one could have a panel of 20 different biased peptide libraries where, in each library, the middle residue is held constant as a given amino acid, but, in each library the constant residue is different, so, collectively, all 20 possible genetically encoded amino acids are explored by the panel.

We note that the term "structural panel" was used in that passage, but "structured panel" was clearly intended, see page

⁵ Unless they were first labeled in some distinct way that would allow them to be separated once more.

10, lines 16 and 22. We have corrected page 10, line 1 accordingly.

The definition noted above refers in turn to the definition of a panel at page 9, lines 33-38. This in turn refers to still earlier definitions on pages 8-9.

All of the peptides of the libraries have the same length. Thus, if the middle residue is the first fixed position, the middle residue in one library aligns with the middle residue of another, and the structured relationship is established by the fact that the middle residue is constant in every library of the panel.

Similarly, in the libraries of claims 32-38 which recite a scanning residue at a "second position", each library will have two constant residues. One of these will be identifiable as the "first position" because a constant residue occurs at its position in every library (although the AA varies from library to library). The other will necessarily be the "second position", and it will be seen that its position varies from subpanel to subpanel.

4E. The terms "first" and "second" are arbitrary but not relative. It is customary in patent practice, when one needs to distinguish between two similar entities, to label one as the "first" such entity and the other as the "second". With regard to explicit recitation of a "peptide sequence", see B above.

5. Prior Art Issues

5.1. Rejection of claims 22, 25 and 28-29 over Pinilla

Pinilla was previously addressed (in connection with claims 21-23) in our May 24, 2000 response. We replaced claims 21 and 23 with new claims 31 and 32, which are not rejected over Pinilla. Claims 22 and 25-27 were amended May 24, 2000 to be dependent on claim 31. Claims 28 and 29 are dependent, through 23 on 31. However, claim 31 has not been so rejected.

The old rejection of claims 21-23 was for anticipation only, while the new rejection (12/5/00) was for anticipation or obviousness.

The Examiner acknowledged that claim 31 is in "closed" form. However, the Examiner does not seem to appreciate the full significance of that form.

Yes, it is true that when Pinilla scans position 5 and 6 in Table 1, the constant residue is in the middle. Indeed, our claim 31 panel is a subset of Pinilla's panel. However, a subset claimed in closed form is not anticipated. Nor was it obvious over Pinilla to use just a subset. Pinilla attached no special significance to the middle 50%. Pinilla instead teaches "walking" the defined position "through the entire sequence of the PS-SCL" (page 225, col. 1).

5.2. Rejection of claims 22, 25, 28-29 over Huffman

The Examiner's 12/5/00 action directs our attention to Huffman, page 6, line 28, and in particular to the sequence $X_1-X_2-X_3-O_4-X_5-X_6$.

This sequence describes a library which has a constant residue in the middle 50%. However, Huffman's panel ("collection") was

OXXXXX
XOXXXX
XXOXXX
XXXOXX
XXXXOX
XXXXXO

which plainly is not limited to the "middle 50%". Hence, the closed form of claim 31 distinguishes Huffman, too. Because Huffman considers all positions to be equivalent, he clearly teaches against a collection in which the scan is limited to a

subset of positions.

5.3. Rejection of claims 32-38 over Spatola

The examiner interprets "first position is fixed for all libraries in the panel and is assigned the same residue for all peptides in a given library" as meaning that "all the libraries in the panel have the same amino acid at the first position". He adds that "the claim does not recite that the amino acid residue in the fixed position of each library is different".

The examiner ignores the language "but libraries of the panel collectively present a plurality of different residues at said first position".

The Examiner consider's Spatola's position 1 to read on our "first fixed position". However, Spatola does not "collectively present a plurality of different residues" at his position 5; all of his libraries have Asp at position 5.⁶

Moreover, Spatola's fixed residue is outside the middle 50%. The Examiner, in response, says that the "middle 50%" is not clearly defined.

We last addressed the definiteness of "middle 50%" on page 12 of our May 24, 2000 amendment. That rejection was not repeated. So we are perplexed by the Examiner's posture.

If Spatola's AA5 is the "first fixed position", then it is outside the "middle 50%". Indeed, it is at one of the far ends. There is no way of construing "middle 50% to include AA5 of a pentapeptide!

Note that even though Spatola made cyclic peptides, Spatola's AA5/D-Asp is identifiable as the pre-cyclization C-terminal. Also note that our claim requires linear peptides.

Attached hereto is a marked-up version of the changes made

⁶ We wish to point out that in our libraries, the "first fixed position" is not an end position of the peptide.

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to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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By: 

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Enclosure

-Clontech Product Catalog entry for MATCHMAKER
Random Peptide Library

-DIVERSE-QUEST hexapeptide, beta-hairpin peptide and alpha-helix
peptide libraries catalogue pages

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification

Paragraph beginning at line 1 of page 10 has been amended as follows:

A "[structural] structured panel" is a panel as defined above where there is some structural relationship between the member libraries. For example, one could have a panel of 20 different biased peptide libraries where, in each library, the middle residue is held constant as a given amino acid, but, in each library the constant residue is different, so, collectively, all 20 possible genetically encoded amino acids are explored by the panel.

In the claims

Claims 27, 30, 32, 33 and 35 have been amended as follows:

27 (twice amended). A structured panel consisting of a plurality of biased combinatorial linear peptide libraries, each library having one and only one constant residue at a position fixed for all peptides in all libraries of said panel, all peptides of said panel being the same length, wherein, in each library, said fixed position is (a) at least five residues from both ends of the peptides or (b) within the middle 50% of the peptides,

wherein the amino acid is assigned to said fixed position is not the same in all libraries of said panel,

each library being a separate [separately screenable] and physically distinct entity from all other libraries of the panel, in which the peptides are displayed on viruses.

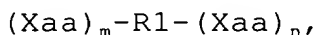
30 (twice amended). A structured panel consisting of a plurality of biased combinatorial linear peptide libraries, each library having one and only one constant residue at a position fixed for all peptides in all libraries of said panel, all

peptides of said panel being the same length, wherein, in each library, said fixed position is (a) at least five residues from both ends of the peptides or (b) within the middle 50% of the peptides,

wherein the amino acid is assigned to said fixed position is not the same in all libraries of said panel,

each library being a separate [separately screenable] and physically distinct entity from all other libraries of the panel in which the peptides are displayed on viruses

wherein said peptides are of the form



where R1 is the amino acid at said first fixed position, and m and n do not differ by more than two,

in which R1 is tryptophan, proline or tyrosine.

32 (amended). A structured panel of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being the same length, each library having exactly two constant residue positions, one at a first position and the other at a second position,

where the first position is fixed for all libraries in the panel, and is assigned the same residue for all peptides in any given library, but libraries of the panel collectively present a plurality of different residues at said first position,

where said first position is (a) at least five amino acids from both ends of the peptides, or (b) is in the middle 50% of the peptides,

where said panel comprises a plurality of subpanels, each comprising a plurality of libraries, and in each subpanel, the location of the second position is constant, but said location varies from subpanel to subpanel so the second positions of said subpanels, collectively scan all residue positions except for

said first position,

where the second position is assigned the same residue for all peptides in a given library but the libraries of a given subpanel collectively present a plurality of different residues at said second position,

where one or more of the other positions of said libraries are variable positions, at which a given library exhibits a plurality of different residues as a result of sequence variation from peptide to peptide,

each library being a separate [separately screenable] and physically distinct [physical] entity from the other libraries of the panel.

33 (amended). A structured panel of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being the same length, each library having exactly two biased residue positions, one at a first position and the other at a second position, the amino acids allowed in each library at said biased positions being only a subset of the set of amino acids allowed at the remaining positions of said library, and also being only a subset of the set of amino acids allowed at that biased position in the panel as a whole,

where the first position is fixed for all libraries in the panel,

where said first position is (a) at least five amino acids from both ends of the peptides, or (b) is in the middle 50% of the peptides,

where said panel comprises a plurality of subpanels, each comprising a plurality of libraries, and in each subpanel, the location of the second position is constant, but said location varies from subpanel to subpanel so the second positions of said subpanels collectively scan all residue positions except for said first position,

each library being a separate [separately screenable] and physically distinct [physical] entity from the other libraries of the panel.

35 (amended). A structured panel of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being the same length, each library having exactly two biased residue positions, one at a first position and the other at a second position, the amino acids allowed in each library at said biased positions being only a subset of the set amino acids allowed at the remaining positions of said library, and also being only a subset of the set of amino acids allowed at that biased position in the panel as a whole,

where the first position is fixed for all libraries in the panel,

where said first position is (a) at least five amino acids from both ends of the peptides, or (b) is in the middle 50% of the peptides,

where each library is obtained by mixing a plurality of different mixed oligonucleotides, each oligonucleotide comprising one fully variable codon and one less variable codon, the position of the less variable codon varying so that said plurality collectively scan also positions other than said first fixed position, said less variable codon encoding the second position of each peptide

each library being a separate [separately screenable] and physically distinct [physical] entity from the other libraries of the panel.